

# Addressing hemolysis in an infant due to mother–infant ABO blood incompatibility

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DOI: 10.3163/1536-5050.96.3.002

## INTRODUCTION

This issue of the *Journal of the Medical Library Association (JMLA)* honors the life of and contributions to medical librarianship of Estelle Brodman, PhD. Dr. Brodman's interests in medical bibliography, automation, international collaboration, education, the history of medicine, and the profession were far reaching, and her ideas reflected innovation and a strong desire to grow the profession and skills of medical librarians [1, 2]. Since that time, medical librarianship has continued to evolve, realizing many of the ideas Dr. Brodman and others advocated. For example, the availability of medical databases and widespread use of computers in libraries have improved library processes and the ability to quickly locate information. With her strong advocacy of lifelong learning, Dr. Brodman also serves as an important role model as a librarian/educator, and she would likely have been pleased to see the profession's emphasis on continuing education and research [3, 4].

As McClure noted in her discussion of Dr. Brodman as a historian, Dr. Brodman found that the study of history "often illuminates the meaning of the present and indicates logical possibilities for the future" [5]. The history of the development of neonatal critical care, like that of medical librarianship, has doubtless been influenced and evolved by pioneering thinkers. One such thinker and contemporary of Dr. Brodman, Mildred T. Stahlman, MD, was also a leader in education, practice, and research in her chosen field, neonatal critical care medicine. In 1961, Dr. Stahlman, known as the pioneer of modern neonatal intensive care, led a National Institutes of Health research project to explore the physiological aspects of the developing fetus and changes that occur at birth [6, 7]. At a critical point in her research, Dr. Stahlman made the groundbreaking decision to adapt a scaled-down respirator, a breathing machine originally developed for polio patients, to assist breathing in an infant born with severe hyaline membrane disease, a lung disease seen in premature infants whose lungs have not yet fully developed. The infant, who previously faced certain death, was able to survive with this first-ever respiratory therapy that gave a viable treatment option for preterm babies with underdeveloped lungs [6, 8]. This groundbreaking research led Dr. Stahlman to develop the first modern neonatal intensive care unit (NICU) at Vanderbilt University Medical Center [6].

Today, NICUs have become an essential part of health care in the United States for critically ill infants and their families, providing constant observation and care for these babies. Premature babies, infants

born earlier than thirty-seven weeks gestation (the typical threshold for defining normal gestation) [9], represent a high percentage of those cared for by a NICU. These babies often have a variety of developmental issues requiring intensive treatment. Given the constantly evolving state of clinical research, NICU teams frequently encounter information needs requiring consultation of the medical literature.

## THE CASE

You are a librarian collaborating with the clinical team in your hospital's NICU, who round at the bedside of a thirty-six-week gestation infant girl. Although the baby was premature, the diagnosis that prompted her admission to the NICU was ABO incompatibility, a condition that can appear in both premature and full-term babies and part of a broader family of conditions that includes Rh incompatibility [10].

The human ABO system includes four blood groups: A, B, AB, and O [10]. Blood cells of individuals with type A or B blood have small molecules on their surfaces called antigens. The human body generates antibodies against whichever blood group antigens it does not have [11]. Humans with group A generate anti-B antibodies; those with group B generate anti-A antibodies; AB individuals have both antigens so they do not produce anti-A or anti-B antibodies; and individuals with type O blood do not have these surface antigens, so they create antibodies against both A and B [11, 12].

If the mother's blood type does not match the fetal blood type (in the current case, this baby is type B and her mother is type O), then the mother's immune system may create antibodies against the fetus's blood type, which then can travel back across the placenta to the fetus [13, 14]. After the baby is born, some of the baby's red blood cells (RBCs) may be coated with the maternal antibodies, leading to destruction of some of the RBCs (hemolysis, also referred to as hemolytic disease of the newborn) by the baby's immune system. The first signs of this kind of hemolysis often include jaundice and high bilirubin levels in the baby's blood (hyperbilirubinemia) [15–17]. Clinicians aggressively treat these symptoms in infants affected by ABO incompatibility, because hyperbilirubinemia can cause serious adverse effects for the baby if left untreated. Such adverse events include kernicterus (brain damage due to high bilirubin), cerebral palsy, or deafness [15]. ABO incompatibility occurs in approximately 15% of all pregnancies, but hemolytic disease of the newborn develops in only 4%. This condition is also more common and often more severe in infants of African descent [10].

**Figure 1**  
Clinician comments

Jaundice, or hyperbilirubinemia, is a common occurrence in the neonatal intensive care unit (NICU) and is normally treated successfully with hydration and phototherapy. However, some more serious hemolytic diseases such as ABO incompatibility cause a much greater level of concern. Bilirubin levels must be watched carefully immediately after birth and for a few days afterward, because treatment must be given urgently in the case of an abrupt rise. Historically, if phototherapy, the first line of treatment, is not effective, the next step would be an exchange transfusion, but such therapy is traumatic for a neonate and introduces the risk of infection.

A previous search conducted by the clinical librarian on the team identified a decision aid in guidelines from the American Academy of Pediatrics (AAP) that noted that the bilirubin level can reach twenty milligrams per deciliter (mg/dL), instead of sixteen mg/dL indicated in our previous protocol, before an exchange transfusion is imminent for a lower-risk infant [21]. Although being able to use the higher level as an indicator buys a little more time to avoid an exchange transfusion, a crucial step would be to investigate if there is an intermediate therapy available if phototherapy is not effective, to be given prior to a blood exchange if necessary. Is it possible or advisable to give intravenous immunoglobulin G (IVIG) to prevent the need for exchange transfusion in some babies? Because we use IVIG to successfully treat infants with infections, can we infer that the infusion of immunoglobulin G might allow the excess waste (bilirubin) to dissipate more quickly? Successful IVIG may prevent potential morbidity and expense, plus complications, of blood exchange. As chief of nurseries, it is critical for me to know if the literature will help weigh risks and benefits of this or any other alternatives.

Before the examination of the literature described in the current case, clinicians in our NICU dealing with jaundice secondary to ABO incompatibility had only a two-tiered therapy protocol: If phototherapy did not correct the jaundice, they had the option to escalate treatment to blood exchange transfusion, with the risks and benefits that accompany this procedure. IVIG now serves as a strong intermediate tier in our protocol, preventing for numerous babies the adverse effects associated with immediately escalating from phototherapy to exchange transfusion.

At birth, this baby's bilirubin is markedly high at 12 milligrams per deciliter (mg/dL) (normal range 0.3–1.9 mg/dL [18]). Her face and abdomen have become yellow in appearance, indicative of jaundice, and phototherapy (light therapy that aids the baby's body in removing excess bilirubin from the blood [19]) and hydration have already been started to treat her jaundice. It is now day of life 2, and her bilirubin level continues to rise (now, 16 mg/dL) despite the interventions. During morning rounds, the team's discussion focuses on the next treatment steps to pursue. The clinical team discusses whether an exchange transfusion (a process by which the infant's blood would be removed and replaced with fresh donor blood or plasma [20]) is necessary now or whether there might be another, less-invasive option to try first. Because exchange transfusion is very traumatic for preterm infants and is associated with numerous and potentially life-threatening complications [20], the team feels it is imperative to consider less intrusive treatments if available and effective. One physician notes that she has seen literature about intravenous immunoglobulin (IVIG) therapy to treat this type of hemolysis. The team asks you to investigate this therapeutic option immediately to support the development of this baby's treatment plan. Figure 1 provides additional commentary from the attending physician (Walsh) on the significance of this question for the practice of neonatal critical care medicine.

## THE CLINICAL QUESTION

Is IVIG a safe and effective alternative to exchange transfusion in a premature infant with hemolysis and hyperbilirubinemia secondary to ABO incompatibility, who has failed phototherapy?

## UNDERSTANDING THE MEDICAL CONCEPTS

In addition to the concepts defined above, it also may be useful to look closer at the human body's immune response and the involvement of immunoglobulin G (IgG, also known as gammaglobulin) to better understand why the team is considering this agent as a treatment option.

Antibodies, also known as immunoglobulins, are one kind of protein found in the blood. These immunoglobulins function as a key part of the body's immune defense system. IgG is one of the most important parts of the immune response: it coats foreign cells so that other cells defending the body are better able to find and destroy the foreign cells [22]. To make IgG available for therapeutic use, donor blood plasma is pooled and purified and then administered to patients intravenously [22]. In the setting of hemolysis due to ABO incompatibility, researchers postulate that IVIG may block the maternal antibodies circulating in the baby's bloodstream from destroying the baby's RBCs, halting the progression of hemolytic anemia [16]. Thus, administration of IVIG may help the baby's body counteract the potential adverse effects of any blood group-related antibodies acquired from the mother during gestation.

## EXPLORING THE LITERATURE

After building your knowledge on the topic, you may find it helpful to use the evidence-based format—patient, population, or problem; intervention or exposure; comparison; outcome (PICO)—to develop and organize your search strategy [23] (Table 1). Basing your strategy on this framework, your search in PubMed may look something like this:

(hyperbilirubinemia[mh] OR erythroblastosis, fetal[mh] OR anemia, hemolytic[mh]) AND immunoglobulins, intravenous[mh] AND infant, newborn[mh]

You try adding in terms for the ABO incompatibility portion of the question from Table 1, but you notice that doing so seems to screen out quite a bit of material, leading you to suspect that you may be risking omitting relevant information, and you return to the broader search strategy. Because this strategy retrieves approximately seventy articles, further limiting seems unnecessary. In considering this retrieval set, you exclude articles in which titles and abstracts indicate topics irrelevant to the case, such as those focusing on other blood incompatibilities that are fairly different from the ABO incompatibility illus-

**Table 1**  
Potential terms for searching PubMed

P	I	C	O
Hyperbilirubinemia [mh]	Immunoglobulins, Intravenous [mh]	Blood transfusion [mh]	Complications [tiab]
Erythroblastosis, fetal [mh]	IVIG [tiab]	Exchange transfusion [tiab]	Morbidity [mh]
ABO blood-group system [mh]		Exchange transfusion, whole blood [mh]	Morbidity [tiab]
Blood group incompatibility [mh]			Mortality [mh]
Bilirubin/blood [mh]			Mortality [tiab]
Bilirubin [tiab]			
Hemolytic disease of the newborn [tiab]			
Hyperbilirubinemia [tiab]			
Jaundice, neonatal [mh]			
Jaundice [tiab]			

Key: P: patient, population, or problem; I: intervention or exposure; C: comparison therapy; O: outcomes of interest; mh: Medical Subject Heading; tiab: title and abstract.

trated by the current case (e.g., Rh hemolytic disease), conditions like parvovirus infection, or intrauterine diagnosis and therapy for the fetus.

After this process of elimination, you have a pool of six articles that report original patient data on IVIG treatment of hyperbilirubinemia due to ABO incompatibility [17, 24–28], two relevant systematic reviews [29, 30], and one recent general review article [31]. Now you are ready to evaluate the quality of the evidence these citations provide by assessing the strength of this primary research on the topic.

By looking at the retrieved prospective studies [17, 24–26], you immediately realize that your topic has not been heavily investigated, and, after reading the abstracts, you note that the studies do not include a large number of infants. Because the retrieval yields no clinical trials conducted in the United States, you consider trials performed in foreign centers, being alert to variations—such as genetic, socioeconomic, and cultural differences—that can affect results when extrapolating and applying to a US NICU population. Even though the centers and investigators represented by the trials are not well known for pediatric research, they form the core of available evidence on the topic.

In addition to these prospective studies, you find two small case studies, one including nine babies [27] and one with three babies [28]. Given the relatively small size of this literature, these two articles may merit a brief mention in your summarization of the literature, though their small size and retrospective nature present challenges to generalizability.

You examine the two systematic reviews more closely to evaluate their relevance and relative strengths and weaknesses. The systematic review completed by Alcock and Liley in 2002 [29] evaluates whether IVIG is effective in reducing the need for exchange transfusion in neonates with isoimmune hemolytic jaundice (“isoimmune,” also “alloimmune,” refers to the development of antibodies in an individual against antibodies from another individual in the same species [30], a broad group of diseases to which ABO incompatibility belongs). Their analysis of three studies meeting their inclusion criteria (one of these studies included ABO incompatibility) indicates that IVIG is associated with a

significant reduction in the need for exchange transfusion in isoimmune hemolytic jaundice; however, the authors emphasize that variability and other methodological concerns regarding the included studies are likely associated with significant limitations to applicability and generalizability. The second systematic review by Gottstein and Cooke examines the same literature with slightly less stringent methodological criteria and time period and arrives at similar conclusions [31].

Examining the references of the general review by Murray and Roberts [32] reassures you that you have found the key items in this area. Also, in the section of the review covering high-dose IVIG, you note that the authors identify late anemia as a potential problem in patients treated with IVIG instead of exchange therapy, because the maternal antibodies remain in the blood after IVIG therapy but are largely removed during the exchange transfusion process. Armed with this knowledge, you can watch for comments on this side effect as you summarize the individual studies for the team.

A brief search of guidelines.gov uncovers a 2004 guideline from the American Academy of Pediatrics (AAP) on the management of hyperbilirubinemia in newborn infants of thirty-five or more weeks of gestation [21]. This guideline includes the following recommendation statement: “Intravenous [gamma]-globulin has been shown to reduce the need for exchange transfusions in Rh and ABO hemolytic disease,” which is followed by a comment on the limited data available to support this recommendation, in line with the paucity of studies you have identified in your literature search.

## SUMMARIZING THE LITERATURE

To provide the team with an overview of your findings, you prepare a concise statement that encapsulates the main points of the topic with pertinent observations on the quality and quantity of the available evidence. For this question, your overall summary (example in Figure 2) may include: ■ commentary on the methodological variation and relatively small amount of data available to address the question, with reference to the two systematic

**Figure 2**

Sample statement describing the overall state of the literature

**The use of IVIG to lower bilirubin levels in an infant with ABO incompatibility**

Although IVIG therapy has been reported in hyperbilirubinemia of Rh hemolytic disease, its use in ABO hemolytic disease has been reported in only a few studies. This literature is characterized by small patient populations and varying methodological characteristics, potentially limiting the generalizability of these results to broader clinical practice. Two systematic reviews, one by the Cochrane Collaboration, note significant methodological issues in this area of the literature [29, 31].

Two randomized trials, a quasi-randomized study, and a prospective single-group trial each found that IVIG administration reduced the need for exchange transfusion in newborns [17, 24–6]. Two case series also note potential benefit for infants with hemolysis due to ABO compatibility [27, 28]. No adverse effects of IVIG administration were noted in these articles; however, these articles note the potential for late development of anemia in babies receiving IVIG instead of exchange transfusion, because the maternal antibodies are not removed from the bloodstream as in exchange transfusion and may lead to later problems; however, late anemia was not observed in these studies.

In addition, guidelines produced by the AAP Subcommittee on Hyperbilirubinemia (2004) state that intravenous immunoglobulin has been shown to reduce the need for exchange transfusions in Rh and ABO hemolytic disease, at a dose of 0.5–1.0 grams per kilogram over 2 hours and repeated after 12 hours if necessary (recommendation 7.1.4) [21].

reviews [29, 30] and the AAP guidelines [21] affirming these issues

■ brief commentary on the included studies and case series to give the team an overall sense of the available evidence on efficacy and safety

■ a note indicating that IVIG has also been used to treat other conditions in neonates (e.g., Rh incompatibility) and that you can provide summary

of this literature as well if the team is interested in exploring broader applicability of this intervention in the NICU

Following your overall evaluation on the topic, you briefly summarize each of the articles you selected, highlighting their relevance to the question. Table 2 provides example summaries, including:

■ the design of each study

**Table 2**

Detailed summaries of included articles

First author (pub date)	Study design	Patients	Methods	Results
Miqdad et al. (2004) [24]	Prospective, randomized trial	112 term babies with ABO hemolytic disease	Newborns were randomized to either: 1. phototherapy plus intravenous immunoglobulin (IVIG) (500 mg/kg) administered between 2 hours and 72 hours (68% receiving IVIG before the age of 24 hours and 94.6% by the age of 48 hours) (n=56) or 2. phototherapy alone (n=56) Follow-up was conducted at 6 and 12 weeks to check hemoglobin and red cell count for development of late anemia	4 babies in the study group and 16 babies in the control group required exchange transfusion ( $P=0.007$ ). Late anemia was not a factor in either group, nor were there any adverse effects related to IVIG administration. There was no significant difference between groups in hospital stay. Study group had phototherapy for 2–7 days (average 3.848 days), and control group had phototherapy for 2–9 days (average 4.402 days), producing a statistical significance of $P=0.036$ .
Alpay et al. (1999) [25]	Randomized, prospective trial	116 infants with ABO and/or Rh incompatibilities who presented with significant hyperbilirubinemia, included 93 with ABO incompatibility, 16 with Rh incompatibility, 7 with ABO+Rh incompatibilities	Infants were randomized to either: 1. phototherapy with high-dose (HD) IVIG (1 g/kg, over 4 h) immediately upon diagnosis (n=58) or 2. phototherapy alone (n=58)	8 exchange transfusions were necessary in the study group, and 22 patients in the control group were transfused ( $P<0.001$ ). Hours of phototherapy and hospitalization were significantly shorter in the HDIVIG group ( $P<0.05$ ), and no side effects of HDIVIG therapy were noted. Authors note that patients should be followed for late development of anemia after HDIVIG therapy.
Tanyer et al. (2001) [26]	Quasi-randomized, prospective trial	61 infants with blood group incompatibility, including 34 with ABO incompatibility	By order of admission, patients received phototherapy plus either: 1. multiple dose IVIG treatment (3 doses 500 mg/kg, 2–4 hour infusion period, during 3 consecutive days) (n=20) or 2. single dose IVIG treatment (500 mg/kg, 2–4 hours infusion period) (n=20) or 3. no IVIG (n=21)	Exchange transfusion was required by no patients in group I, 3 patients in group II, and 7 patients in group III ( $P<0.05$ ). No adverse effects of IVIG were noted.
Hammerman et al. (1996) [17]	Prospective, single-group study	26 babies with blood group incompatibility, including 22 with ABO incompatibility and 4 with Rh incompatibility	Infants with ABO incompatibility received 500 mg/kg infused over 2 hours if bilirubin reached 13 mg/dl during first 24 hours after birth or if bilirubin reached 16 in infants >24 hours of age; if bilirubin continued to rise to 20 mg/dl, exchange transfusion was initiated	19 babies responded with decreased serum bilirubin, including 17 ABO babies and 2 Rh babies. All 7 nonresponders received exchange transfusion. No side effects of IVIG therapy were noted.



- the number of patients and their conditions (as some of the studies included Rh incompatibility as well)
- methods of each study, including dosage and administration schedule for IVIG and other treatment information (e.g., concurrent phototherapy)
- study results, including the number of patients requiring exchange transfusion and other outcomes measured (e.g., hospital stay), and any adverse events

## CONCLUDING REMARKS

Because of the detrimental effect of exchange transfusion on an infant recipient, finding a safe and effective alternative would not only be beneficial for the present patient, but potentially for many who follow. A less invasive therapy would prevent the trauma and possible complications endured by infants with hemolysis and their families.

Sackett's classic definition for evidence-based medicine as the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [33] notes the importance of both clinical expertise and the best-available evidence in determining the ideal pathway for patient care. This case serves as an example of augmenting clinical judgment with evidence, however limited, from the literature and underscores the value of each. The literature serves to confirm clinician assumptions regarding the utility of the therapy, while clinical judgment dictates a need to explore options to reduce potential adverse events for this child.

At the authors' institution when this question was originally asked in 2003, this practice of evidence-based medicine resulted in the NICU team's decision to treat this patient with IVIG, successfully restoring her bilirubin level to normal. Subsequently, this therapy was adopted as part of the NICU's protocol for hyperbilirubinemia with ABO incompatibility and is now frequently employed in babies whose bilirubin continues to increase despite phototherapy. Thus, the integration of evidence from the literature with the expertise of the clinical team, including the librarian as a key member, led to an exciting and important advancement for infant care in the NICU.

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